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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,144	08/04/2003	Jin Lee	TRA-006.01	5095

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
06/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,144	LEE ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,13,14,16-28,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,14,16-28,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-1-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 3-27-09 is acknowledged.

Claims included in the prosecution are 11, 13-14, 16-28 and 32-33.

In view of the amendment to claim 11, the 112, second paragraph rejection is withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 11, 16, 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abra cited above, in view of Ye et al (5,997,899).

Abra discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60-65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

What is lacking in Abra is the repetition of the heating and cooling. Abra does not teach the use of DPPC for the formation of liposomes

Ye et al while disclosing a method of preparation of liposomes teach that three

cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

To employ three cooling and heating cycles in the method of preparation of liposomes of Abra would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC instead of HSPC taught by Abra would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues the following:

> "In order to establish a primafacie case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. Once an Examiner has made a prima facie case of obviousness, secondary considerations, if they are present, must also be considered in an obviousness determination. See MPEP § 2145. Rebuttal evidence to a prima facie showing may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Assuming arguendo herein that a primafacie case of obviousness has been made, Applicants respectfully assert that the unexpectedly improved results disclosed in the instant application establish the nonobviousness of the pending claims. As noted above, the pending claims have been amended to make clear that the lipid complex-forming lipids are phosphatidylcholines selected from the group consisting of DPPC, DSPC, and mixtures thereof. Percent entrapment and drug to lipid rations for formulations of

> DPPC or DSPC with cholesterol and cisplatin are provided in Table 4, on page 10, in the instant application. When three cycles of warming and cooling have occurred, the percent of cisplatin entrapment for DPPC and DSPC increases from 4.3% to 21.3% and 2.5% to 14.5%, respectively. In other words, the claimed method results in a almost 5-fold increase in encapsulation of cisplatin when DPPC is used and an almost 6-fold increase in encapsulation of cisplatin when DSPC is used. Neither Abra nor Ye teach nor suggest that heat and cooling would result in a 5- to 6-fold increase in encapsulation. Therefore, because of the unexpectedness of such a large increase in encapsulation, the Applicants respectfully request the Examiner withdraw the rejection of the pending claims as unpatentable over Abra in view of Ye."

These arguments are not persuasive. First of all, it would appear from Example 4 on page 10 of the specification, that a single experiment was conducted and no statistical evaluation was made. Secondly, the claims are drawn to platinum compound and no cholesterol is recited whereas the experiment in Example 4 was performed using cisplatin a combination of cholesterol and either DSPC or DPPC in specific ratios. Finally, the results are to be expected and not unexpected based on the teachings of Ye that percent incorporation of the active agent increases with an increase in the carbon chain length of the fatty acid of PC (Table 5 on col. 13). Applicant's arguments therefore, are not persuasive.

3. Claims 11, 13-14, 16-28 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi (US2002/0182248) in combination with Abra and Ye et al both cited above.

Yamauchi teaches a method of encapsulating a drug in liposomes by mixing the lipids with an aqueous solution of a drug, heating it above the transition temperature of the membrane and then cooling it. The preparation is extruded through a membrane

filter (0043, 0051 and 0057). What is lacking in Yamauchi is the use of cisplatin as the drug and also repeating the steps of changing the temperature in two or more cycles.

Abra as pointed out above, discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60 to 65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

Ye et al as pointed out above, while disclosing a method of preparation of liposomes teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

The use of a platinum drug such as cisplatin in the method of Yamauchi would have been obvious to one of ordinary skill in the art since Yamauchi teaches that any drug can be encapsulated and the reference of Abra shows the knowledge in the art of encapsulating cisplatin. To employ three cooling and heating cycles in the method of preparation of liposomes of Yamauchi would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments with regard to Abra and Ye. Applicant's only other argument is that Yamauchi fails to remedy the deficiencies of Abra and Ye and Yamauchi provides no teaching that heat and cooling would result in a 5 to 6 fold increase in encapsulation. This argument is not persuasive since as already pointed out above, Abra teaches heating and cooling and Ye teaches three cooling and heating cycles and also an increase in encapsulation using the claimed phospholipids.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK